

HYPOVOLEMIA INDUCED ORTHOSTATIC HYPOTENSION IN PRESYNCPAL  
ASTRONAUTS AND NORMAL SUBJECTS RELATES TO HYPO-SYMPATHETIC  
RESPONSIVENESS

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Running Head: Hypovolemia, orthostatic hypotension and adrenergic responsiveness

Key words: sympathetic, tilt test, low salt diet

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## ABSTRACT

Spaceflight-induced hypovolemia requires astronauts to mount a hyper-sympathetic response in order to complete a tilt test on landing day. We tested the hypothesis that experimentally-induced hypovolemia, in the absence of spaceflight, also requires a hyper-sympathetic response during tilt. We studied 17 subjects during normovolemia and hypovolemia. Plasma volume, tilt tolerance, supine and standing arterial pressure, heart rate and plasma norepinephrine (NE) levels were measured. During hypovolemia tilts, subjects who increased their norepinephrine release above that during normovolemia tilts were significantly more likely to complete the test. These results indicate that adequate norepinephrine release during tilt can overcome the hemodynamic compromises of hypovolemia. This model may be used to identify susceptible astronauts prior to flight so that prospective, individualized countermeasures can be developed.

## INTRODUCTION

The adaptations of humans to the conditions of spaceflight include profound physiological changes that can have deleterious effects upon landing. It is difficult to predict these changes before flight because the unique physiological challenges of spaceflight often unmask symptoms that would not manifest in these healthy astronauts under normal conditions. A major physiological adaptation to spaceflight is a reduction in circulating blood volume [1-3], which has a significant effect on orthostatic tolerance. Other systems must compensate for the volume loss if orthostatic tolerance is to be maintained after landing. During postflight testing of orthostatic tolerance, only those who can mount an extra-ordinary sympathetic response are able to maintain upright blood pressures during stand or tilt tests. A substantial percentage of astronauts cannot mount such a response and experience severe orthostatic hypotension and presyncope [1-4]. The ability to predict, before flight, those astronauts that will have orthostatic hypotension on landing day would be a major breakthrough in the effort to develop appropriate countermeasures. To date, the only predictor of postflight orthostatic hypotension and presyncope in an individual astronaut has been the tilt test outcome from a prior flight [5]. Preflight identification of susceptibility is difficult because, prior to flight, large sympathetic responses are not needed to maintain upright posture. Thus incidents of presyncope preflight are very rare in these normal healthy astronauts. We theorized that, since loss of blood volume is a large driver of postflight orthostatic hypotension, it may be possible to reproduce the landing day presyncope by reproducing the landing day hypovolemia. In a ground-based study, we used a regimen of an intravenous dose of furosemide plus a low salt diet to induce hypovolemia. We tested the hypothesis that the incidence of presyncope during upright tilt testing would be the same during hypovolemia as it is on landing day, and that the underlying cause of presyncope

would be inadequate compensatory sympathetic responses. If true, we would be able to predict before flight which individuals would become presyncopal after spaceflight, so that countermeasures could be prescribed prospectively for them.

## METHODS

This study was approved by the Johnson Space Center Committee for the Protection of Human Subjects. All subjects signed informed consent documents. Subjects were 12 men and 5 women, aged  $40.9 \pm 2$  years. Six of these were astronauts (five men and one woman), for whom we were able to compare their previous preflight and postflight tilt test outcomes with their current normovolemia and hypovolemia tilt test outcomes. Subjects came to the laboratory on three occasions, with tilt tests occurring on days 1 and 3. On day 1 (normovolemia day), subjects had consumed a minimum of 2 grams of NaCl every day for a week. On day 2, subjects had voluntarily reduced their salt intake for the prior three days and initial hypovolemia was achieved by the slow infusion of 0.5 mg/kg of furosemide at a rate of 4 mg/min. This was followed by 36 hours of a very low sodium diet (10mEq/day). We chose this regimen to avoid the acute vasoactive effects of furosemide and to achieve a steady state hypovolemia [6]. Day 3 (hypovolemia day) began 40 hours after the furosemide infusion. Days 1 and 3 were separated by at least two weeks, and for female subjects were always performed during menses.

On each study day, subjects had abstained from taking any medications for the previous 24 hours, had not eaten a heavy meal within 4 hours, had consumed a light snack within 2 hours, and had not exercised maximally within 24 hours. Subjects were placed supine on a tilt table and instrumented for ECG, brachial artery pressure (Dinamap) and beat-to-beat finger arterial pressure (Finapres). An intravenous catheter was placed in an antecubital vein for blood draws. The subject then rested on the table for 20 minutes, at which time plasma volume was measured

using a carbon monoxide rebreathing technique [7,8]. A blood sample was drawn for plasma norepinephrine levels. Measurements of heart rate and arterial pressure were obtained for 5 minutes, after which the tilt table was inclined to 80° upright. Measurements continued for 15 minutes and a final blood sample was drawn. If presyncopal symptoms caused early termination of the tilt test, the table was returned to the supine position while blood was drawn immediately. Catecholamines were later measured by radioenzymatic assay [9].

### *Statistics*

All results are presented as means  $\pm$  SE. The effect of hypovolemia on plasma volume, blood pressure, heart rate and delta norepinephrine (upright minus supine) was tested using repeated measures analyses of variance. The dependent measures used in these analyses were first tested for normality and equal variance using the Kolmogorov-Smirnov test and the Levene Median test. A Cox proportional hazards regression, with jackknifed standard errors to account for the small sample size and repeated measures, was used to determine which factors were most important in determining tilt survival time [10]. Estimates of the regression coefficients and the baseline hazard function were then used to generate tilt-time survival curves for various combinations of change in plasma volume and delta norepinephrine.

## RESULTS

### *Plasma Volumes*

Plasma volume indexes (PVI, plasma volume / body surface area), is shown for all subjects in Figure 1 for both the normovolemia and hypovolemia days. Plasma volume index was significantly decreased on the hypovolemia day ( $P < 0.0001$ ). The loss ranged from -0.02 to -0.59 L/m<sup>2</sup>.

[Figure 1 here]

### *Supine Arterial Pressure and Heart Rate*

There were no differences in arterial pressure between the normovolemia and hypovolemia days, but heart rate was higher during hypovolemia. Baseline systolic and diastolic pressures were  $114 \pm 3$  mmHg and  $66 \pm 2$  mmHg during normovolemia and  $114 \pm 3$  mmHg and  $69 \pm 2$  mmHg during hypovolemia ( $p = \text{NS}$ ). Baseline heart rate was  $56 \pm 2$  bpm during normovolemia and  $63 \pm 3$  bpm during hypovolemia ( $P < 0.0005$ ).

### *Orthostatic Tolerance*

Of the six astronaut subjects who participated in this study, the four who became presyncopal during tilt tests on landing day also became presyncopal during tilt tests on the hypovolemia day. The two astronauts who did not become presyncopal on landing day did not become presyncopal during tests with hypovolemia. Unfortunately, no preflight or postflight plasma volume or norepinephrine data were available so comparisons were not possible.

Figure 2 presents original tracings during normovolemia and hypovolemia for one non-presyncopal subject (top two panels) and one presyncopal subject (bottom two panels). The presyncopal subject maintained upright tilt for only five minutes on the hypovolemia day.

[Figure 2 here]

### *Norepinephrine Responses*

[Figure 3 here]

Figure 3 presents supine and standing plasma norepinephrine levels for the same two subjects are presented in Figure 2. During normovolemia the two subjects had similar increases in norepinephrine levels during upright tilt. During hypovolemia, they had similar supine plasma norepinephrine levels, but the presyncopal subject had no additional increase in response to tilt,

while the non-presyncopal subject had a greater than two-fold increase. This same trend holds true for the entire group of subjects (figure 4).

[Figure 4 here]

### *Combined Responses*

The survival curves in Figure 5 show that the probability of surviving a 15 minute tilt test decreases with increasing plasma volume loss and increases with the increasing norepinephrine release. Plasma volume losses of 0.2, 0.4 and 0.6 L/m<sup>2</sup>, and plasma NE increase of 0 (panel A), 250 (panel B), 500 (panel C) and 750 pg/ml (panel D) were chosen for illustration. The summary of Figure 5 is that adequate sympathetic compensation can protect tilt survival even in the face of profound hypovolemia.

[Figure 5 here]

## DISCUSSION

This study describes a very important finding; that if astronauts and normal subjects are subjected to experimentally-induced hypovolemia that reproduces spaceflight-induced hypovolemia, they will self-separate into two groups, those who do and those who do not become presyncopal during an upright tilt test. In the astronauts whom we tested under both conditions, the hypovolemia reproduced the occurrence of post-spaceflight presyncope with 100% fidelity. Moreover, the mechanism of presyncope in both conditions appears to be the same; the failure to mount the hyper-sympathetic response needed to overcome the hemodynamic compromise caused by hypovolemia. Using this model, we showed that even with a plasma volume loss of 30%, subjects who can release enough norepinephrine still have an 80% probability of completing 15 minutes of upright tilt.

This model can provide new opportunities for the study of mechanisms of blood pressure control. By driving subjects into a compromised hemodynamic state, we can measure the limits of sympathetic responsiveness. The model offers the means to determine which astronauts may be susceptible to postflight orthostatic hypotension prior to their first flight, so that countermeasure treatments can be individualized and prescribed prospectively. Within patient populations the model could be useful in the study of the interaction of volemic state and the sympathetic nervous system in both hypotension and hypertension.

### *Spaceflight Relevance*

Our group has published several reports regarding post-spaceflight orthostatic hypotension that include data from over 100 astronaut subjects. In each study we found subtle preflight differences between the responses of astronauts who were and were not destined to become presyncopal during tilt tests on landing day [1-4]. However, the differences were not



great enough to allow us to predict postflight presyncope. The current study is a breakthrough in this effort.

Many attempts have been made by this laboratory and others to restore plasma volume losses in astronauts prior to their return to Earth [11,12]. To date those attempts have been unsuccessful. All of the astronauts who have been subjects in our flight studies had consumed the required fluid load of salt tablets and water (or its equivalent) prior to landing. Still they average a 9% loss of plasma volume after both short [2,4], and long-duration flights [13]. It is clear that this is the major underlying factor for orthostatic hypotension. In fact, we have shown that restoration of plasma volume in bedrest eliminates post-bedrest orthostatic intolerance [11]. The key to postflight orthostatic tolerance is actually the degree to which the sympathetic nervous system can compensate for the volume loss [2,4,14]. Therefore, our more recent countermeasure development efforts have focused on  $\alpha$ -adrenergic agonists to supplement sympathetic responses. The  $\alpha$ -agonist midodrine has been successful in preventing postflight orthostatic hypotension [15], but it may not be appropriate for all crew members. The new hypovolemia model may be used as a quick screening test to compare relative efficacy of new countermeasures, so that more choices will be available to crews. The model could also be effective in identification of susceptible crew members and could eventually be used as a selection criterion for flight assignments.

This model already has allowed us to compare the effects of hypovolemia alone with the effects of spaceflight on left ventricular mass, an area of some controversy. It had been suggested by some that decreases in left ventricular mass after spaceflight might indicate cardiac atrophy associated with spaceflight and bedrest [16-18]. However, our hypovolemia model effected the same decrease in left ventricular mass as that seen on landing day [19]. This

suggests that the postflight reductions in mass may be secondary to simple physiologic fluid redistribution. Other cardiovascular changes after spaceflight, such as decreased aerobic capacity, must also have a large hypovolemic component. The same hypovolemia model could be used to separate the hypovolemia effect from the “deconditioning” effect.

It is important to note that this model may “under-predict” susceptibility after longer duration missions, which last months rather than days. We have shown that even crew members who were not presyncopal during tilt tests after short Shuttle flights become presyncopal after long flights [13]. It is thought that a central remodeling occurs as flight progresses due to lack of afferent baroreceptor input, such that efferent sympathetic responses may be blunted [3]. The usefulness of this hypovolemia model for longer flights will be mostly in preflight comparisons of the efficacy of various countermeasures or combinations of countermeasures.

### *Summary*

We report a new model which uses hypovolemia to force humans into a hemodynamic state that is similar to that after spaceflight. This model can be used to test candidate countermeasures for postflight orthostatic hypotension and to identify crewmembers who will be most susceptible to that symptom on landing day.

### *Limitations*

Data published by this laboratory show that female astronauts are more susceptible to orthostatic hypotension after spaceflight [4], however, the results from this study do not clearly show gender differences during hypovolemia. This may be explained by the different mechanisms of plasma volume reduction. The female astronauts have plasma volume losses after flight that are three times greater than those of their male crewmates, probably due to their different center of gravity [20]. This contributed importantly to their susceptibility. In the

current study, the hypovolemia was induced pharmacologically and there were no differences in plasma volume losses between men and women. This is an important consideration in studies of this type.

## ACKNOWLEDGEMENTS

The authors wish to thank all the subjects who underwent this rigorous protocol. This study was supported by the NASA grant NAS98-HEDS-02-424 and M01RR00827 and M01-RR02558 from the NCRR. We also thank Dr. Dominick D'Aunno, who administered all drugs and Dr. Alan Feiveson who helped with the statistical modeling.

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## Figure Captions

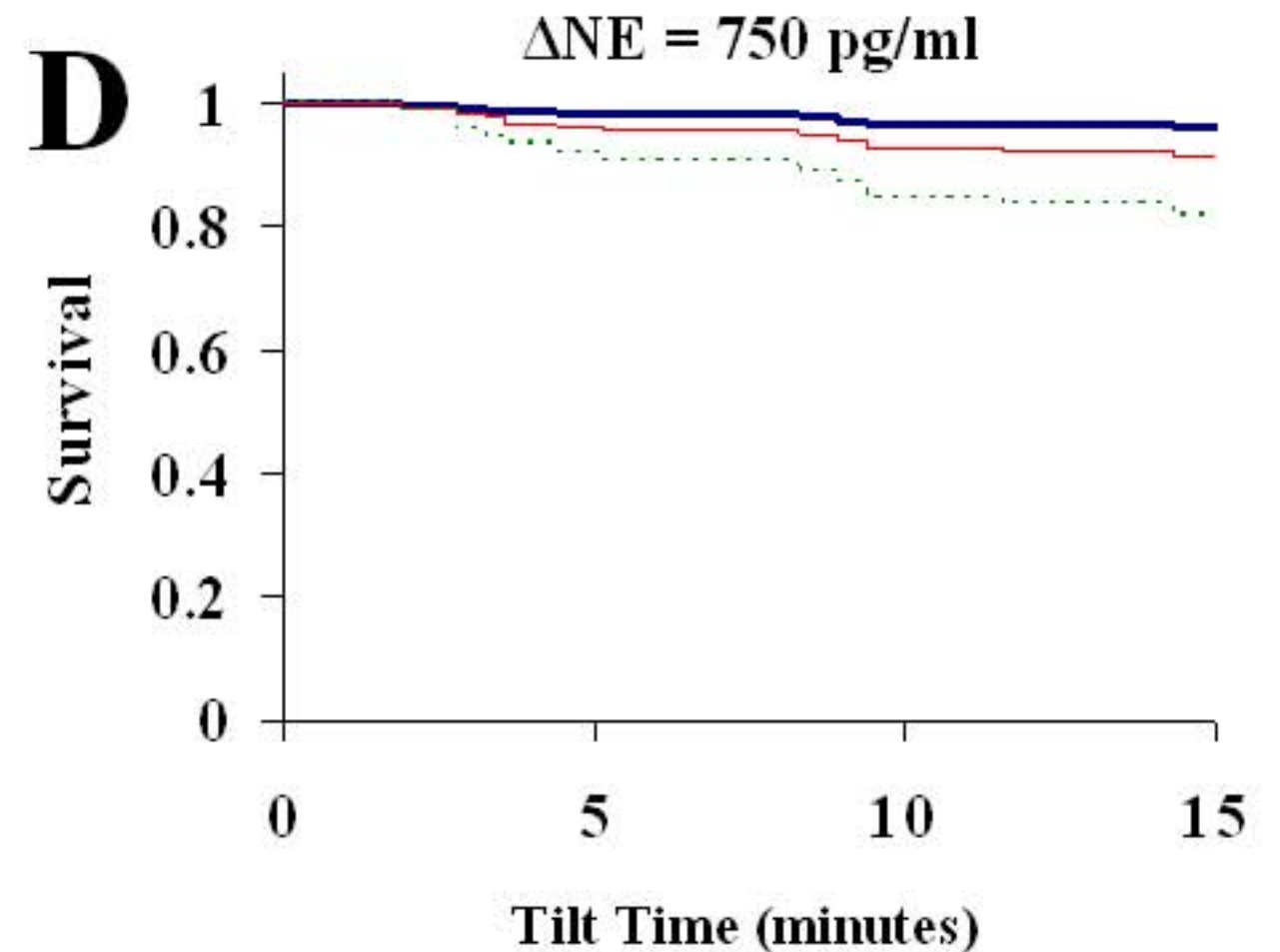
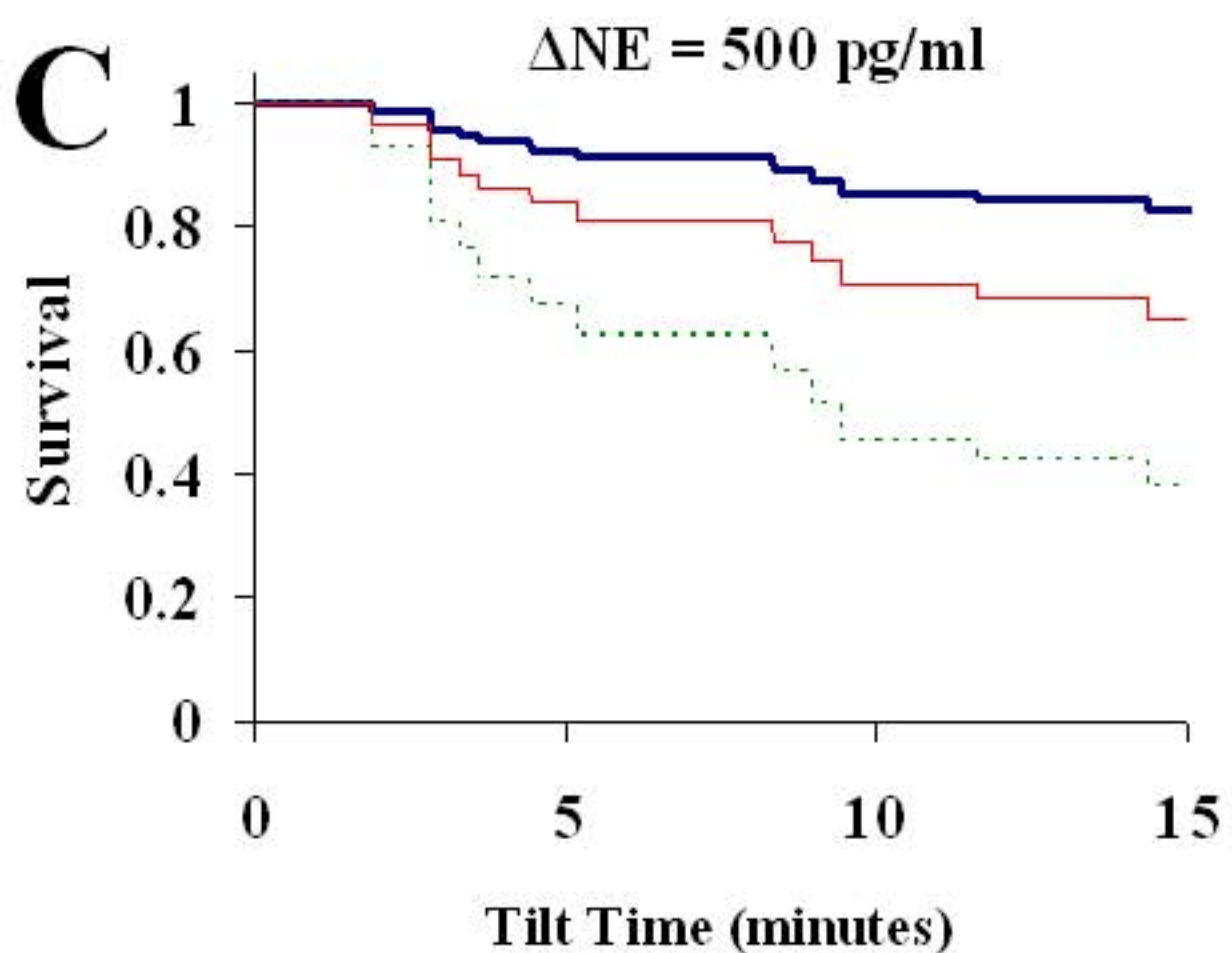
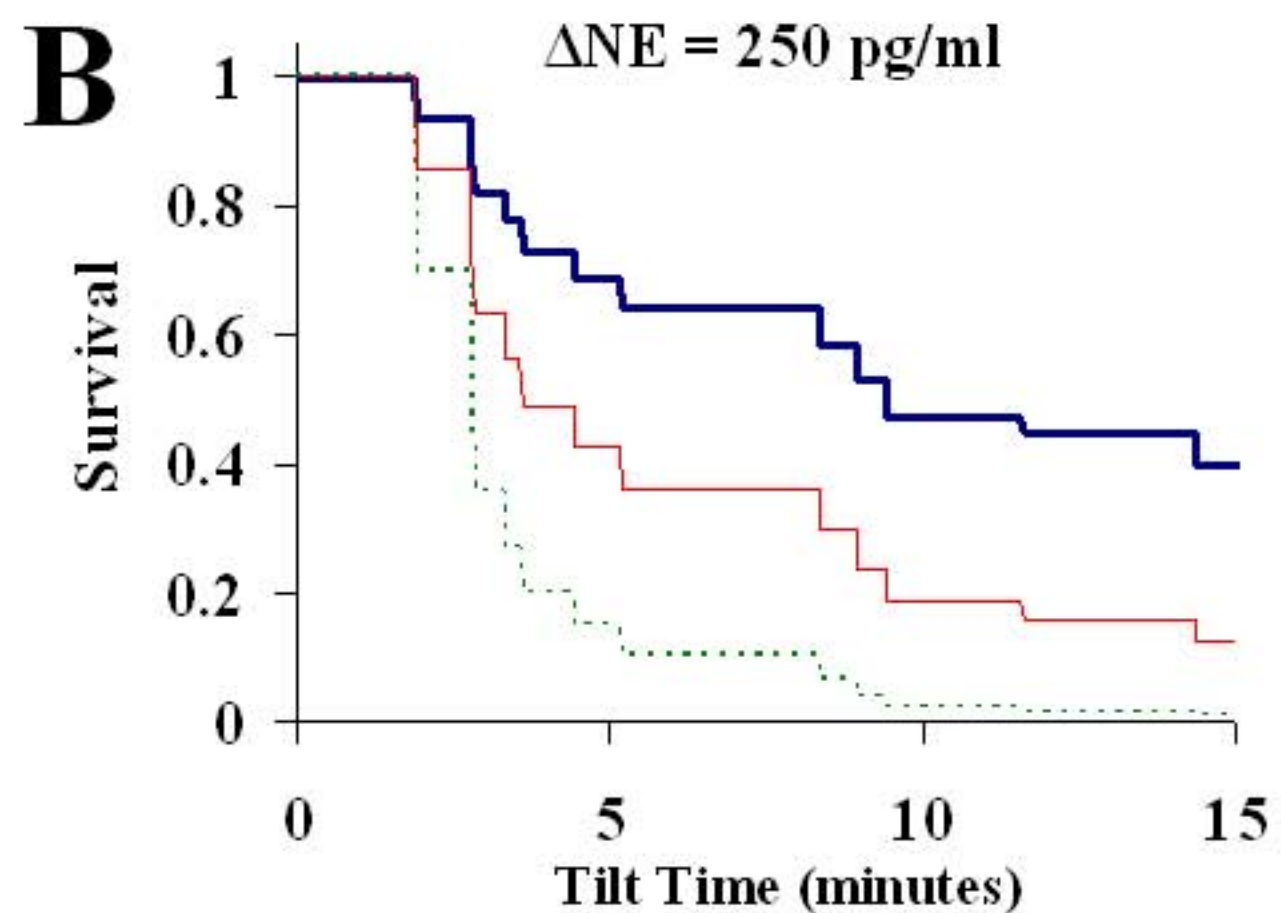
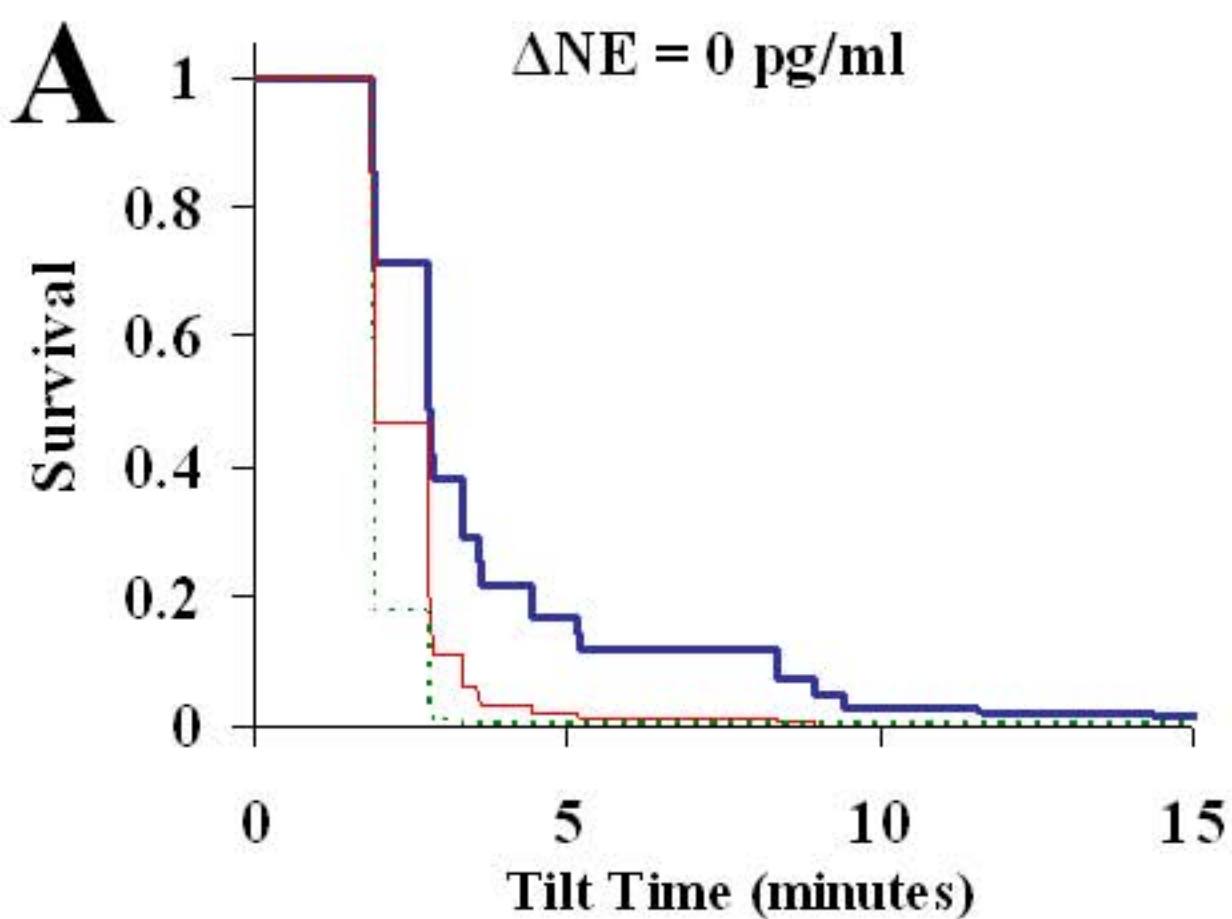
Figure 1. Plasma volume index (plasma volume normalized by body surface area) is shown for all subjects on the normovolemia (left) and hypovolemia (right) days.

Figure 2. Original tracings of arterial pressure and heart rate from tilt tests during normovolemia and hypovolemia in one non-presyncopal subject (top) and one presyncopal subject (bottom). Note that the presyncopal subject remained upright for the entire test on the normovolemia day, but only withstood five minutes upright on the hypovolemia day. The heavy arrows begin at the time of tilt.

Figure 3. Norepinephrine responses to tilt during normovolemia and hypovolemia in non-presyncopal and presyncopal subjects (right). Previously published preflight and postflight norepinephrine responses to tilt have been re-plotted and are presented for comparison on the left (11). Note the similarity between the change from preflight to postflight with that from normovolemia to hypovolemia.

Figure 4. Tilt-induced increase in norepinephrine for presyncopal (black) and non-presyncopal (white) subjects during normovolemia (left) and hypovolemia (right).

Figure 5. Cox proportional hazard analysis prediction of tilt survival based on level of hypovolemia (PVI Loss: [ ——— ]thick blue = 0.2 L/m<sup>2</sup>; [ ——— ]thin red = 0.4 L/m<sup>2</sup>; [ - - - - ]dashed green = 0.6 L/m<sup>2</sup>) and sympathetic responsiveness (tilt-induced norepinephrine release: **A** = 0.0 pg/ml; **B** = 250 pg/ml; **C** = 500 pg/ml; **D** = 750 pg/ml)



—  $\Delta PVI = 0.2$  L/m<sup>2</sup>    —  $\Delta PVI = 0.4$  L/m<sup>2</sup>    - - -  $\Delta PVI = 0.6$  L/m<sup>2</sup>

